REMARKS

Claims 1-36 currently are pending, however claims 7-8 and 12-33 are withdrawn. Claims 1-6, 9-11 and 34-36 stand rejected.

The Office has requested that claims 7-8 and 12-33, drawn to non-elected subject matter, be canceled with this response. Applicants are cancelling these claims herein.

Applicants acknowledge the Office's withdrawal of the rejection of claims 1-6, 11 and 34-36 as anticipated by Winkler et al., as well as the withdrawal of rejections on grounds of double patenting and indefiniteness.

Claims 1-6, 9-11 and 34-36 are rejected on grounds of obviousness over Winkler '195 and Fodor et al. The Office first indicates that the Winkler reference teaches polymer substrate array production, first providing a support having a conduit (channel) with an inlet and an outlet. The claims here recite (as amended) a support body which comprises at least one channel which comprises a conduit with a top, a bottom and two sides, and an inlet and an outlet. As the Winkler document describes and the drawings of Winkler clearly show, the prior Winkler devices and methods uniformly involve a planar substrate 401 which is held against a separate channel block 407. The channel or groove 409 is formed <u>between</u> these two separate parts. See col. 9, lines 17-20, col. 12, lines 3-4, col. 17, lines 35-38, col. 26,

lines 19-48 and Figure 16, for example. Therefore, Applicant submits that the Winkler '195 patent does not teach a support with a conduit that has a top, bottom and two sides, as well as an inlet and outlet.

The Office also refers to specifically immobilizing building blocks on predetermined positions in the channel(s). The Winkler document specifically refers to a substrate on which the arrays are synthesized, which is separate from the channels formed by the channel block. See col. 9, lines 6-23, which describes formation of channels over the substrate by placement of a separate channel block while synthesis occurs not in the channel block but on the substrate. This is another difference in the methods claimed, which require synthesis in channels of the support body and synthesis in these channels.

On page 5, lines 9-17 of the Office Action, the Office refers to a substrate that provides a three-dimensional surface area for synthesis, referencing col. 14 and the Figures. The substrate on which synthesis takes place in Winkler, however, is "preferably flat," but may contain raised or depressed regions on which synthesis takes place. Col. 10, lines 23-26. The substrate does not contain channels. Channels are formed when the flow channel of the channel block contacts the substrate. Therefore, the substrate on which synthesis takes place does not

have channels on or in it, and the Winkler channels do not comprise a substrate such as is recited by the present claims, since the substrate does not have channels. In Winkler, channels are formed over the substrate by a moveable channel block such that the area where fluid moves over the substrate is changed when the channels are moved to a different area on the substrate, to create "flow patterns" on the substrate. The claims here recite a support which contains channels (including top, bottom and both sides) in which the synthesis takes place.

The Office refers to Winkler as teaching a fluid-tight conduit with a top, bottom and two sides (page 6, lines 1-2 of the Office Action), however the substrate on which synthesis takes place is separate from the channels of the channel block. Therefore, in Winkler the support/substrate does not contain the channels. In section iii, page 6, the Office refers to "reference channel embodiments that include tubing and capillaries." Regardless of the laundry list of forms the substrate support may take, the substrate and its surface form a support on which to carry out the reactions. Col. 10, lines 27-28. Flow paths are formed or placed on or adjacent to the substrate. Col. 10, lines 29-30. The channels therefore are up against the substrate and not a part of the substrate, regardless of the surface shape of the substrate. Thus, regardless of

Winkler's teaching of a channel, nowhere does Winkler teach providing a support body that contains a channel which comprises a conduit with a top, bottom and two sides.

The Office Action also states that the Winkler reference teaches monitoring synthesis by fluorescent intensity mapping, citing cols. 28-29. The Winkler method involved completing synthesis and then testing for the presence of completed peptides by staining with FITC-conjugated antibodies. This is not monitoring of the synthetic process as claimed here. The claims have been amended herein to make this monitoring clearer. Claim 1 now recites that the illumination position (predetermined reaction positions) are monitored by computer using the detector matrix. This monitoring takes place during synthesis of the array to confirm that the desired reaction areas are being exposed to light, not after the end of array synthesis to detect binding of antibodies to the completed array. Winkler does not teach any monitoring of the position of illumination by a detector matrix, nor does it teach anywhere, or even hint, that the support is to be positioned between a programmable light source matrix and a detector matrix.

The Office concedes that Winkler does not teach this arrangement, but relies on the Fodor International application for teaching a computer-controlled system (computer programmable

light source matrix) to determine the binding pattern. The Office refers to disclosure in Fodor of a reactor system with a transparent channel, monomers that are bound by illumination and a computer monitor, and even refers to the support being "arranged between a programmable light source [ ] and a detector (e.g. CCD)." The Office does not provide an exact location in Fodor for this teaching concerning the arrangement, however. Applicant submits that nowhere in Fodor is this arrangement taught or even suggested. The Figure which depicts the arrangement of the components to the device, Figure 10, clearly shows that the illumination matrix 1002 and the detection matrix 1012 are on the same side of (above) the substrate and that light is illuminated and detected from only the upper side of the substrate in the Figure. The substrate is <u>not</u> positioned between the illumination and detection devices, see Figure 10 and pages 54-57, which discuss Figure 10. Compare Figure 3 of the present application, which shows the positioned arrangement and the channels of a preferred embodiment.

In summary, none of the art cited by the Examiner provides a device in which the support contains channels in which synthesis is made, none provides an arrangement wherein the illuminated support is placed between the illumination source and the detector, and none provides any mechanism to monitor the

illumination position. The Office therefore has failed to meet the first requirement of a prima facie case of obviousness: all elements of the claim must be taught or fairly suggested by the art.

Nor would there be any motivation to modify and combine the Winkler and Foder references to achieve the present invention. The most that one could achieve when combining the two disclosures of Winkler and Fodor is a system for making arrays using a mask where light emitted from fluorescent labels on the array can be detected by a device placed on the same side of the substrate as the illuminating device. Nothing in either reference or their combination guides the reader to use the detector to monitor the synthesis of the array from "underneath" the array (i.e., on the opposite side from which the substrate is illuminated. See Figure 3 of the present application. Both cited references use a mask technology preferably and employ methods where illumination and detection are performed on the same side of the planar array substrate. Because the claimed methods are not even mentioned anywhere in the cited art, there is no motivation to modify them in the way which would be required to achieve what is claimed here. Therefore, the Office also has failed to meet the second requirement for a prima facie case of obviousness: there is no motivation to combine and modify

this art to achieve what the inventors here have achieved. There also is no reasonable expectation that the methods here would be successful given that the methodology of the cited art uses mask technology which is not used by the inventors and a different arrangement of the components.

Applicant therefore requests withdrawal of this rejection for the reasons, in summary, that several elements of the claims are missing from the cited art in combination, there is no motivation or suggestion to modify their teachings to achieve what is claimed and there is no expectation of success if this were done. No matter how the teachings of Winkler and Fodor are combined, there is no suggestion of placing the substrate (array) between an illumination matrix and a detection matrix or a support body that contains a channel that has a top, bottom and two sides as shown in Figure 3.

Claims 1-6, 9-11 and 34-36 are rejected as obvious over the above cited references in combination with Yeung. The Office cites Yeung as disclosing the advantageous use of a parallel capillary arrays in screening analytes "in the DNA context." Applicants reiterate the remarks made above with respect to the previous rejection based on Winkler and the Fodor international application.

Further, Yeung does not even relate to methods for providing a support for determining analytes. It is a capillary electrophoresis method where analytes in solution are electrophoretically separated and then detected, for example by fluorescence. No array support or illumination matrix are used, no receptors are synthesized by Yeung and illumination and fluid flow are not monitored. The Yeung device excites the molecules and detects emitted fluorescence after electrophoretic separation is complete, but does not illuminate using a matrix or monitor the illumination process. In this respect it is similar for Winkler and Fodor, which also detect fluorescence of labeled molecules (after synthesis) and which also do not illuminate using a matrix or monitor the illumination process. Yeung also does not position a support between an illumination and detection matrix. Therefore, the combined art still lacks required claim elements.

Yeung relates to a completely different technology and therefore would not be combined with the other cited art. Even if it were combined, however, it does not make up for the deficiencies of Winkler, Fodor and their combination. None of the references even involve an illumination matrix or detection or monitoring of the illumination process. Like in Winkler and Fodor, the exact position and location of the illumination device

on particular regions of the array being synthesized is not even important to the function of the method so there is no motivation to monitor it. In Winkler and Fodor the array is produced with generalized illumination and a mask that blocks light. There is no reason to monitor the position of an illumination device that shines light on the entire area. Also, in Yeung the entire electrophoresis capillary is illuminated. In both cases, fluorescence emanating from areas of the array or the electrophoresis capillary are detected.

The Office is equating the DNA arrays of the present invention (or of Winkler, for example) with an array of capillaries which are used to detect DNA when arguing to combine the references. The "DNA context" referenced to in the Office Action in equating these two methods is fallacious since Yeung relates to an array of illuminated tubes and the invention relates to an array of DNA which is created by selective, monitored illumination by an illumination matrix.

The Office maintains that Yeung's arrays are relevant to synthesis of DNA arrays because both the inventive DNA arrays and Yeung's electrophoresis method are used for purposes of screening. The present claim 1 is directed to a method of making a support containing polymeric receptors. Yeung's methods involves filling a capillary with electrophoresis gel. The DNA

arrays on a biochip are used for screening binding. Yeung's methods are used for separation of DNA. Since the claims here relate to methods for synthesizing an array of polymers and Yeung has absolutely no disclosure related to this subject matter, Applicant maintains that Yeung is not relevant to the present invention regardless of the fact that DNA can be separated by capillary electrophoresis.

The Office states that Winkler suggests using capillaries as substrates for DNA synthesis to make arrays for screening, and Yeung teaches using arrays of capillaries to screen analytes "in the DNA context," and therefore the skilled artisan would have been motivated to use arrays of capillaries (Yeung) to make DNA arrays. This logic is irrelevant to the complete lack of teaching in any of the cited references, alone or in combination, of a number of claim limitations as discussed above. In any case, "the DNA context" is used by the Office as an umbrella term to imply that any method involving DNA is substantially equivalent to any other method involving DNA. A method for <u>separating</u> DNA in a capillary is not equivalent to a method for <u>synthesizing</u> DNA on a capillary merely because both relate generally to DNA.

Applicant requests that the examiner withdraw this rejection because the Office cannot make out even one of the three required

elements for a prima facie case of obviousness. The totality of the cited art, no matter how combined, still lacks several claim elements: (1) a support body that contains a conduit having a top, a bottom and two sides and a reaction position in the support body; (2) a support that is arranged between a programmable light source matrix and a detector matrix; (3) a programmable light matrix; and (4) monitoring of the illumination position by computer using the detection matrix. There is no motivation provided by any or all of the references to synthesize DNA in such a support body conduit, to rearrange the device to place the support (DNA or other array) such that it is illuminated from one side and the illumination is detected from the other side, i.e., between the illumination and detection matrixes, or to monitor the position of illumination during array synthesis. Moreover, there is no reasonable expectation that such changes would result in a successful method of synthesizing polymer arrays.

Claims 1-6, 9-11 and 34-36 are rejected as indefinite for use of the term "fluid tight." Applicants have amended the claims herein to avoid use of this term and therefore request that this rejection be withdrawn.

Claims 1-6, 9-11 and 34-36 are rejected under the written description requirement of 35 U.S.C. §112, first paragraph for

recitation of the term "fluid tight." As discussed above, Applicants have deleted this term and therefore request that the rejection be withdrawn.

Claims 1-3, 5-6, 9-11 and 34-35 are rejected as anticipated by Fodor, U.S. Patent No. 5,424,186 ("the '186 patent"). In order to make out a case of anticipation, the Office is required to cite an art reference that teaches each and every limitation of the claims rejected. M.P.E.P. §2131. Applicant submits that the Office cannot meet this standard.

As discussed above, claim 1 has been amended for purposes of clarifying what is intended to be claimed. The '186 patent is cited for teaching a method involving a preferably transparent substrate and a support body which together form a channel that has a top/bottom and two sides. It is not cited for teaching a support body that has all four of a top, a bottom and two sides.

The Office cites the '186 patent for teaching monitored synthesis, citing Figures 4, 23 and 24 and columns 35-36. This monitoring is stated to use a computer programmable light source matrix to determine the pattern of binding. Figure 4 shows illumination of regions not covered by a mask. It does not relate to monitoring of the array synthesis. Figure 23 is a schematic diagram showing an embodiment that lacks a detector and which has a computer that receives information from the peptide

synthesizer, but not the illumination source (see arrows). Notably, the device of Figure 23 also does not show a light source matrix but rather a light source and a mask.

Figure 24 is a flow chart that shows control of the steps for synthesis such as flow of reagents, but does not show any monitoring of illumination position or information from a detector regarding illumination. Columns 35-36 discuss the computer control of reagent flow. The computer is provided signals indicating the beginning of a photolysis cycle or optionally from the keyboard. The computer coordinates action of the peptide synthesizer, translation stage and light source. The light source is controlled in terms of turning it on and off at desired times, but is not monitored in terms of the positions that are illuminated by the light source. Optionally, the position of the mask is checked by using alignment marks on the mask and a CCD device that can be used to align these marks. At no time is a detector used to monitor the illumination positions.

Therefore, Applicant submits that the '186 patent does not disclose a system wherein the illumination position is monitored by the detection matrix and thus cannot anticipate claim 1.

The Office then cites pages 22-29 of the Fodor international application as well as its examples and claims. Applicant submits that this is not proper when making a rejection on

grounds of anticipation by a single reference and the rejection should be withdrawn for this reason alone. The specific pages from the international application, however, likewise does not disclose or even suggest monitoring of illumination position. The claims of the international application refer to computer control of flow of reagents and illumination, but do not teach monitoring of illumination position.

The Office then refers to the detector of the Fodor international application, which applicant submits is improper in making out a case of anticipation by a single reference, the '186 patent. However, pages 60-63 of the Fodor international application relate to detection of fluorescence from already-synthesized arrays which were labeled with fluorescent streptavidin and do not relate in any way to monitoring the illumination position of an illumination matrix. Figure 35 of the '186 patent is then cited for a detector. This Figure is the same as Figure 10 of the Fodor international application, which is discussed above. This Figure shows that the illumination device and the detection device are on the same side of the array and therefore do not meet the limitation of claim 1(a), final clause.

In summary, the Office Action states that the synthesis is monitored, however the computer of the '186 patent does not

monitor the illumination position using a detection matrix. The computer of the '186 patent controls turning on and off parts of the system and can be used to align the mask, but does not even receive signals from the detector matrix, thus making it impossible for this system to monitor the positions being illuminated as is claimed herein. Applicant therefore submits that the '186 patent does not anticipate each and every claim element, either alone or in combination with the Fodor international application on which the Office also relies. Applicant therefore requests that this rejection be withdrawn.

Claims 1-6, 9-11 and 34-36 are rejected under 35 U.S.C. §103(a) as obvious over the Fodor '186 patent in view of Yeung. As discussed above, the '186 patent does not describe or even suggest a system or method in which an optically transparent or other carrier for array synthesis is placed between an illumination matrix and a detection matrix so that the illumination positions are monitored using the detection matrix. Yeung does not even relate to the art of DNA array synthesis and so cannot edify the reader as to how the '186 patent could be modified to add these features. Yeung describes capillaries for electrophoresis, not an array of DNA. Yeung does not involve synthesis of DNA in any step and so cannot provide any motivation even to use its capillaries for making DNA array, much less

suggest to the person of skill that the '186 patent system should be changed to monitor illumination position during DNA synthesis. Yeung does not teach or suggest a detection array that monitors illumination position. It only detects fluorescent label from electrophoresced DNA samples. The '186 patent also uses the detector in this manner, to detect fluorescent-labeled DNA, but not to monitor illumination position during synthesis of the array. Thus, the combination of references cited here lack required claim elements.

Applicants respectfully submit that the Fodor and Yeung references would not be considered to relate to the same subject matter by the person of skill merely because both involve DNA ("the DNA context"). One is a method of <u>synthesizing</u> DNA arrays optionally in or on a capillary and the other is a method of <u>separating</u> DNA in capillaries. Yeung teaches that capillaries are good for separating DNA by electrophoresis, it does not suggest or provide motivation to synthesize DNA on the capillaries. Therefore, the person of skill would not connect these two separate technologies. Yeung would not be considered relevant to the skilled person attempting to synthesize DNA in an array since it does not relate in any way to DNA arrays or even DNA synthesis.

Even if a skilled person did try to combine the '186 patent and the teachings of Yeung, however, there would be no expectation of success in achieving what is claimed here. The most one could achieve, as discussed in the Office Action at page 19, final paragraph, is a method from the '186 patent (DNA array synthesis without monitoring of illumination position, in which both the illumination device (and mask if present) and the detector are on the same side of the substrate on which the array is bound) where the substrate is an electrophoresis capillary array of Yeung. Merely adding the idea of using capillaries for an array substrate does not achieve the limitations of the claims here, so there is no reasonable expectation of success in achieving the invention of the present application. The Office has conceded as much with its own statements concerning what Yeung adds to the '186 patent.

Applicant submits that the Office has not met even one of the three criteria necessary to make out a prima facie case of obviousness here. The combined art lacks several claim elements (for example, substrate position and monitoring of illumination position), would not be combined by the person of skill since they relate to completely different arts (DNA array synthesis and DNA electrophoresis), and which even if combined would not result in a reasonable expectation of successfully achieving what is

claimed here. Applicant therefore requests that this rejection be withdrawn.

The claims have been amended herein for the sake of clarity as to what is intended to be claimed and to provide better antecedent basis. Claim 1 now more clearly recites the position of the optically transparent support containing a channel (with top, bottom and sides) between a programmable light source matrix and a detector matrix and more clearly recites that the position(s) illuminated by the illumination source matrix are monitored by computer using the detection matrix. Applicants submit that no new matter has been added. Page 42, line 35 to page 43, line 1 and page 45, lines 3-7, teach the position of the support between the light matrix and detector matrix. See also Figure 3. Optical transparency of the support is discussed at page 15, lines 24-30 and page 12, line 11, which teach transmission of excitation and light waves by the support body. Illumination of specific selected positions is taught at page 16, lines 24-35, and page 19, lines 17-27 which discusses deliberate control of the matrix points or light source elements to create a two-dimensional illumination pattern. Monitoring the illumination position during synthesis, using the detection matrix is discussed at page 17, lines 1-2, page 39, lines 10-13 and page 43, lines 28-34. The specification teaches using a

detector to ensure that the correct positions are illuminated to avoid error. See, for example, page 37, lines 22-25, which discusses avoidance of faulty assignment of light signals, overlap, etc., and page 43, lines 28-34, which discuss control of the light source matrix by a computer that collects and evaluates data from the light detector component of the system, a feature lacking in the combined prior art as cited. These claim elements also are supported by previous versions of the claims. Therefore, no new matter is added.

Applicant requests reconsideration of the claims as amended.

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